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Assignment of the Absolute Configuration of Goniodomin A by NMR Spectroscopy and Synthesis of Model Compounds

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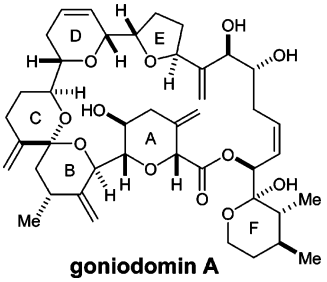
ABSTRACT



The complete absolute configuration of goniodomin A, an actin-targeting polyether macrolide isolated from the marine dinoflagellate *Alexandrium hiranoi*, was established from analysis of ROESY experiments and coupling constants, synthesis of suitable model compounds for NMR spectroscopic comparisons, degradation experiments, and correlation with synthetic reference compounds.

Goniodomin A (**1**, Figure 1) was isolated as a potent antifungal agent by Murakami and co-workers from the dinoflagellate *Alexandrium hiranoi* (formerly *Goniodoma pseudogoniaulax*) collected in the rock pool at Jogashima in Japan in 1988.[1] More recently, it was reported that the dinoflagellate *Alexandrium monilatum* produced goniodomin A.[2] The gross planar structure of goniodomin A was established by Murakami and co-workers on the basis of the NMR studies to be a novel polyether macrolide, which contains a 6/6-spiroacetal, a dihydropyran, a tetrahydropyran, 17 stereogenic centers, and an additional hemiacetal ring appended at C31.[2] However, the relative and absolute stereochemistry of goniodomin A remains to be solved.

Goniodomin A has been found to cause the conformational change of actin to modulate skeletal actomyosin ATPase activity,[3] and the potent stimulation of the actomyosin

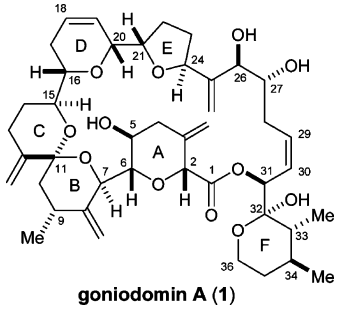


Figure 1. Structure of goniodomin A

(1) Murakami, M.; Makabe, K.; Yamaguchi, K.; Konosu, S.; Walchli, M. R. *Tetrahedron Lett.* **1988**, *29*, 1149−1152.

(2) Hsia, M. H.; Morton, S. L.; Smith, L. L.; Beauchesne, K. R.; Huncik, K. M.; Moeller, P. D. R. *Harmful Algae* **2006**, *5*, 290−299.

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ATPase activity induced by goniodomin A appears to be highly sensitive to the troponin/tropomyosin complex.[4] Furthermore, goniodomin A has been demonstrated to induce largely different modulation of actomyosin ATPase activity between ventricular and atrial muscles.[5] It has also been reported that goniodomin A causes morphological changes in human astrocytoma cells by increasing the filamentous actin content.[6] In 2002, goniodomin A was reported to inhibit angiogenesis by the inhibition of endothelial cell migration and basic fibroblast growth factor-induced tube formation and to be active in vivo.[7] These results clearly indicated that goniodomin A has profound effects on reorganization of the cytoskeleton.

The important biological properties of this compound as well as its intriguing molecular structure prompted us to embark on the complete stereochemical assignment, including the absolute configuration and total synthesis of goniodomin A. Recently, Fujiwara and co-workers reported their synthetic approach to the stereochemical assignment of goniodomin A.[8] Herein, we describe the complete stereochemical assignment of goniodomin A, including the absolute configuration, based on detailed 2D NMR analysis of the natural product, synthesis of suitable model compounds for NMR comparison, degradation experiments, and correlation with synthetic reference compounds.

The relative stereochemistry of the macrolide ring, containing the A- to E-rings, and the isolated hemiacetal F-ring was determined through analysis of proton coupling constants and ROESY data of **1** (Figure 2). Due to the conformational restrictions imposed by the presence of one spiroacetal ring and three ether rings incorporated into the macrolide ring, compound **1** appears to be a relatively rigid ring. In particular, transannular ROESY correlations observed for **1** were keys to assignment of the relative stereochemistries.

C2−C15 Portion (A). A large coupling constant (J = 8.4 Hz) between H5 and H6 indicated a diaxial arrangement for these protons,[9] and thus an equatorial orientation of 5-OH. H2 was also assigned as axial on the basis of ROESY correlations between H2/H4a and H2/H6. H7 and 9-Me were assigned as axial by a ROESY cross-peak H7/9-Me. A ROESY correlation between H10a and 12 = CHa indicated the equatorial orientation of the C11−C12 bond, thereby assigning the acetal oxygen in the C-ring as axial. A ROESY correlation was observed between H13b[10] and H15, suggesting that the C-ring adopts a twist-boat conformation and that

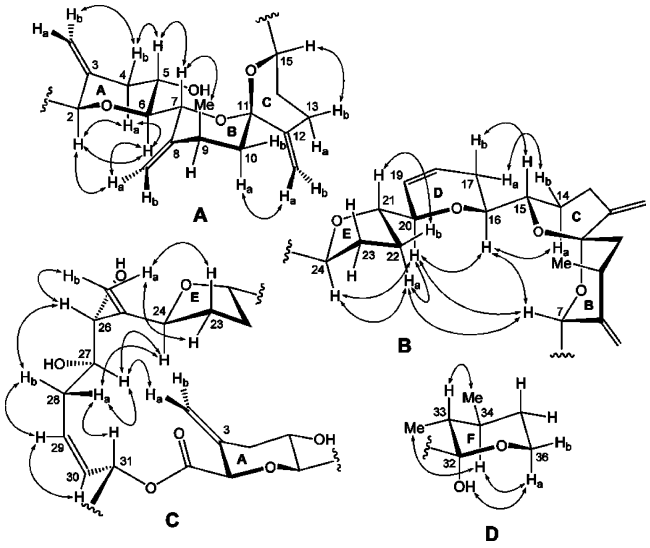

Figure 2. ROESY correlations for the C2−C15 (**A**), C7−C24 (**B**), C24−C31 (**C**), and C32−C36 (**D**) portions of goniodomin A (**1**) (600 MHz, C_6D_6, acetone-d_6, or CD_2Cl_2)

the stereochemistry of H15 must have a pseudoaxial orientation. The relative configuration between the A- and B-rings was assigned by a large coupling constant (J = 8.4 Hz) between H6 and H7, indicating an anti arrangement for these protons,[10] and ROESY correlations H5/H7, H6/8 = CHa, and H2/8 = CHa.

C15−C24 Portion (B). The D-ring was readily assigned to be a 2,6-cis-substituted dihydropyran by a ROESY correlation between H16 and H20. The relative stereochemistry of the C-/D-ring juncture was assigned on the basis of a large coupling constant (J = 9.6 Hz) between H15 and H16 and ROESY cross-peaks H14a/H16, H14b/H17a, and H15/H17b. Furthermore, H7 showed significant ROESY cross-peaks to H16 and H20, allowing us to interrelate the relative stereochemistries of the BC- and D-rings, as shown. A large coupling constant (J = 9.0 Hz) between H20 and H21 revealed an anti arrangement for these protons, and ROESY correlations between H20/H22a and H20/H24 allowed the E-ring to be a 2,5-trans-substituted tetrahydrofuran. In addition, an unobserved ROESY correlation between 19H and 22-CH_2 indicated that C19 and C22 have an anti arrangement, which was also supported by a transannular NOE between H7/H22 observed in the ROESY spectrum.

C24−C31 Portion (C). The relative stereochemistry of the 26,27-diol in **1** was unambiguously determined by its conversion to the corresponding 26,27-*O*-isopropylidene derivative **2** (Scheme 1). A threo relationship of 26,27-diol was established by a large coupling constant (J = 8.4 Hz) between H26 and H27 and observed NOE data of acetonide **2**, as shown. The ^{13}C NMR chemical shifts for the dimethyl groups on the dioxolane ring (27.7 and 27.2 ppm, respectively), which were typical values for a 1,2-threo-diol system,[11] also supported the assigned configuration. Coupling

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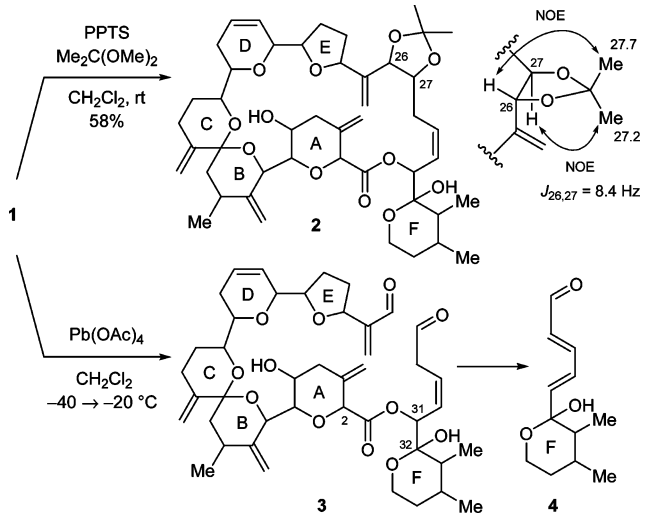
(8) (a) Fujiwara, K.; Naka, J.; Katagiri, T.; Sato, D.; Kawai, H.; Suzuki, T. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1173−1186. (b) Katagiri, T.; Fujiwara, K.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2008**, *49*, 233−237.
(9) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866−876.
(10) $J_{H13a,\ H13b}$ = 12.6 Hz, $J_{H13a,\ H14}$ = 4.5 Hz, $J_{H13a,\ H14'}$ = 3.6 Hz, $J_{H13b,\ H14}$ = 10.8 Hz, $J_{H13b,\ H14'}$ = 10.8 Hz (900 MHz, acetone-d_6).
(11) Dana, G.; Danechpajouh, H. *Bull. Soc. Chim. Fr.* **1980**, 395−399.

Scheme 1. Chemical Derivatization of Goniodomin A



constants ($J_{26,27}$ = 7.8 Hz, $J_{27,28b}$ = 9.6 Hz, and $J_{27,28a}$ < 1 Hz) and ROESY correlations between 25 = CHa/23-CH_2, 25 = CHb/H26, H24/H27, H24/H28a, H26/H28b, and H27/H28a of **1**, allowed us to interrelate the relative stereochemistries of the E-ring and the C26−C28 acyclic portion. Furthermore, the stereochemical relationship between C27 and C31 was assigned on the basis of ROESY correlations H28a/H31 and H27/3 = CHa.

C32−C36 Portion (D). A large coupling constant (J = 11.0 Hz)[12] between H33 and H34 indicated a diaxial arrangement for these protons and an equatorial disposition of both methyl groups at C33 and C34. The acetal hydroxy group at C32 was assigned as axial based on observation of a long-range ω-coupling to H33 and a ROESY correlation to H36a.

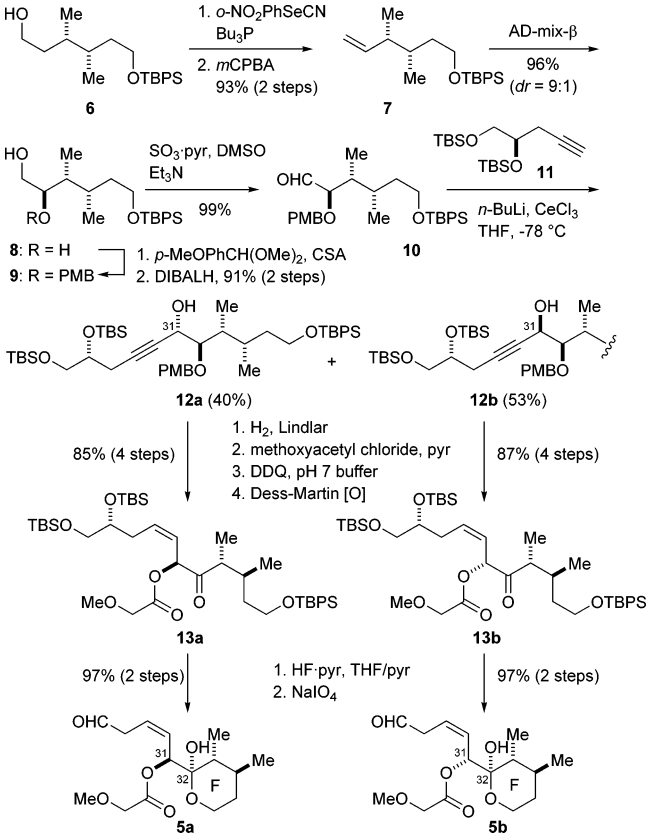
These NMR-based analyses revealed the relative configurations of the entire rigid macrolide ring and the isolated F-ring. The remaining relative stereochemistry of C31/C32 was deduced from an observed weak ROESY cross-peak between H30 and H33. However, the presence of 32-OH precluded the use of a vicinal coupling constant between ring-juncture protons in clearly assigning the relative stereochemistry of C31/C32. Therefore, we attempted to confirm the deduced stereochemistry by comparing the NMR data of a degradation product with those of suitably designed model compounds. After considerable experimentation, it was found that treatment of goniodomin A with $Pb(OAc)_4$ delivered dialdehyde **3** (Scheme 1), which was immediately subjected to NMR experiments due to its extremely labile nature. Upon standing even at low temperature, compound **3** gradually decomposed to produce $\alpha,\beta,\gamma,\delta$-unsaturated aldehyde **4**.[13]

(12) The coupling constant was determined from a decoupling experiment.

(13) Degradation product **4** existed as an approximately 4:1 mixture of a hemiacetal form and the corresponding hydroxyl ketone in C_6D_6 solution. The corresponding acid part could not be isolated, probably due to its instability.

We next designed diastereomeric model compounds **5a** and **5b**, whose syntheses are summarized in Scheme 2. The

Scheme 2. Synthesis of Diastereomeric Models **5a** and **5b**



known compound **6**[14] was converted to terminal olefin **7** according to the procedure of Grieco.[15] Asymmetric dihydroxylation using AD-mix-β afforded diol **8** in high yield and good diastereoselectivity (96% yield, dr = 9:1). Selective protection of the secondary alcohol in **8** as the PMB ether was performed by the *p*-methoxybenzylidene acetal formation, followed by its reductive ring-opening. Oxidation under Parikh−Doering conditions[16] afforded aldehyde **10**, which was then treated with an alkynyl cerium reagent derived from alkyne **11**[17] (*n*-BuLi, THF, −78 °C; then $CeCl_3$, −78 → 0 °C) to afford a diastereomeric mixture of alcohols **12a** and **12b** in 40% and 53% yield, respectively. These alcohols were readily separated by flash column chromatography, and the stereochemistry at C31 of each compound was determined by modified Mosher analysis.[18] Lindlar reduction of **12a**, protection of the alcohol as its methoxyacetate, and removal

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of the PMB group, followed by Dess−Martin oxidation, afforded ketone **13a** in 85% overall yield. Removal of the silyl ethers with HF·pyridine and oxidative cleavage of the vicinal diol furnished the desired model compound **5a** (97%, two steps). According to the same sequence of reactions, diastereomeric alcohol **12b** was also transformed to aldehyde **5b**.

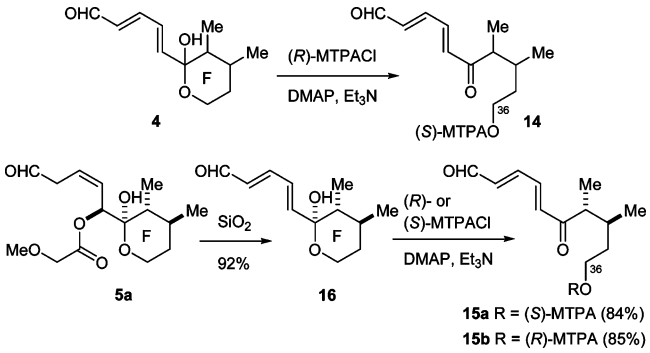
The ^{1}H NMR chemical shift values of H31 and H33 for model **5a**, not for **5b**, matched well those observed for the degradation product **3** (Table 1), allowing for the confirmation of the relative configuration of C31/C32, as depicted in **5a**.

Table 1. Selected ^{1}H NMR Data of the C27−C36 Region in Degradation Product **3** and Synthetic Models **5a** and **5b** (500 MHz, Acetone-d_6)

	3	**5a**		**5b**	
position	δ_H	δ_H	$\Delta\delta$	δ_H	$\Delta\delta$
27	9.72	9.71	0.01	9.70	0.02
28	3.48	3.44	0.04	3.46	0.02
	3.62	3.60	0.02	3.57	0.05
29	5.98	5.93	0.05	5.94	0.04
30	5.75	5.73	0.02	5.73	0.02
31	5.69	5.66	0.03	5.59	**0.10**
33	1.21	1.20	0.01	1.44	**−0.23**
34	1.67	1.66	0.01	1.69	−0.02
35	1.27	1.23	0.04	1.27	0.00
36	3.55	3.56	−0.01	3.57	−0.02
	3.89	3.89	0.00	3.92	−0.03
33-Me	0.96	0.94	0.02	0.93	0.03
34-Me	0.89	0.88	0.01	0.92	−0.03

Finally, to determine the absolute stereochemistry at C33 and C34, a degradation product **4** was converted to the corresponding (*S*)-Mosher ester **14**. Thus, treatment of **4** with (*R*)-MTPACl (DMAP, Et_3N, CH_2Cl_2) effected acetal ring-opening to afford the (*S*)-MTPA ester **14** (Scheme 3). In contrast, model compound **5a**, unstable as naturally derived **3**, was subjected to silica gel chromatography to afford dienal **16** (92%), which was converted to the two authentic (*S*)- and (*R*)-MTPA esters (**15a** and **15b**), respectively. The ^{1}H NMR data of (*S*)-MTPA ester **14** derived from the natural specimen was completely identical with those of synthetic (*S*)-MTPA ester **15a** (Figure 3), thus establishing the absolute configurations at C33 and C34 as 33*R* and 34*S*. Considering all of these data, we can now assign the absolute stereostructure of goniodomin A, as represented in **1** (Figure 1).

Scheme 3. Synthesis of (*S*)-MTPA Ester **14** and (*S*)- and (*R*)-MTPA Esters **15a** and **15b**



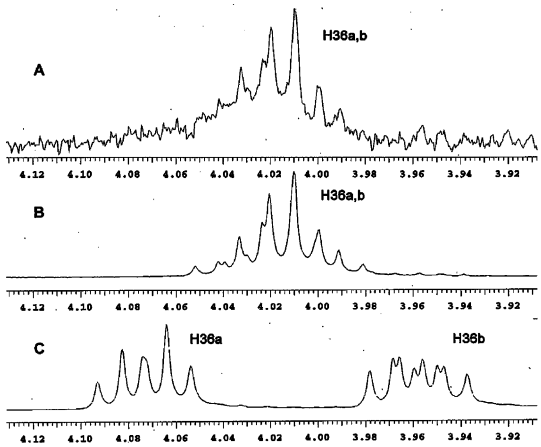


Figure 3. Partial ^{1}H NMR spectra (600 MHz, C_6D_6) of (*S*)-MTPA ester **14** (A), (*S*)-MTPA ester **15a** (B), and (*R*)-MTPA ester **15b** (C).

In conclusion, the absolute configuration of goniodomin A has been defined on the basis of detailed 2D NMR studies, synthesis of suitable model compounds for NMR spectroscopic comparisons, degradation experiments, and correlation with synthetic reference compounds. The present study provides a foundation for total synthesis of this intriguing molecule. Further studies toward the total synthesis of goniodomin A are in progress and will be reported in due course.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1** in C_6D_6, acetone-d_6, and CD_2Cl_2; COSY, ROESY, TOCSY, HSQC, and HMBC spectra; experimental procedures; spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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